## *Remarks*

Entry of the present amendment and reconsideration of this application is respectfully requested. New claims 28-42 have been added. Accordingly, claims 28-42 are active in the application. Claims 16-18 and 21-23 are pending but withdrawn. Claims 1-15, 19, 20 and 24-27 are canceled without prejudice or disclaimer.

Previous claim 1 has been split into new claims 28 and 29. Support for new claims 28 is found, *inter alia*, at specification page 11, lines 10-19. Support for new claims 29 is found, *inter alia*, at specification page 24, line 25.

New claim 30 most closely corresponds to previous claim 5.

New claim 31 most closely corresponds to previous claim 6.

New claim 32 most closely corresponds to previous claim 6.

New claim 33 most closely corresponds to previous claim 2.

New claim 34 most closely corresponds to previous claim 5.

New claim 35 most closely corresponds to previous claim 5.

New claim 36 most closely corresponds to previous claim 6.

New claim 37 most closely corresponds to, and is a broader embodiment of previous claim 8.

New claim 38 most closely correspond to previous claim 8.

New claim 39 most closely corresponds to previous claim 9.

New claim 40 most closely corresponds to previous claim 10.

New claim 41 most closely corresponds to previous claim 13.

New claim 42 most closely corresponds to previous claim 14.

These changes are believed to introduce no new matter, and their entry is respectfully requested.

Based on the above amendment and the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding objections and rejections and that they be withdrawn.

***The Rejections under 35 U.S.C. § 103(a)***

At Office action paragraph 6, claims 1, 5-7 and 24 are rejected under 35 U.S.C. § 103(a) are being unpatentable over:

1. Banker and Rhodes, editors, Modern Pharmaceutics, Fourth Edition., 2002, pages 394 and 399,
2. Fumihiro *et al.*, JP 62-288534,
3. Hunik, WO 2000/37669,
4. Makino *et al.*, US 4,948,788,
5. Craig *et al., J. Pharmaceut. 179*: 179-207 (1999) and
6. Kim *et al., J. Pharm Sci 87*:931-935 (1998).

In addition, at Office action paragraph 14, claims 2, 8-10, 13-15 and 25-27 are rejected as being unpatentable over documents 1-7 as above, as applied to claim 1, and also

7. FDA Guide to Inspections of Lyophilization of Parenterals (said to be available online at http://www.fda.gov/ora/inspect_ref/igs/lyophi.html as of February 28, 1997; and

8. West, *Science 107*: 398 (1948).

Applicants respectfully traverse both these rejections, and Examiner's comments thereon, and respectfully request reconsideration.

***Banker, Hunik and Fumihiro***

*Inter alia*,

1. Banker is relied on as disclosing that "[m]any drugs are too unstable - either physically or chemically - in an aqueous medium to allow formulation as a solution, suspension, or emulsion, and that instead, the drug is formulated as a dry powder (Banker page 394, column 2). Banker is also relied on as disclosing that it is generally known that vitamins, including vitamin B12 (of which methylcobalamin is the active form) are not very stable and that degradation is observed on storage.

2. Hunik is relied on as disclosing that methylcobalamin is known to be unstable to light in isolated form and is easily transformed to hydroxycobalamin in aqueous solution.

3. Fumihiro is relied on as disclosing stable freeze-dried preparations comprising vitamin B12.

At Office paragraph 10, Examiner states:

The skilled artisan, recognizing the instability of methylcobalamin (as taught by *Hunik*) would have been motivated to formulate methylcobalamin as a dry powder (as taught by *Banker and Rhodes*), specifically by freeze-drying (as taught by *Fumihiro et al*).
Examiner also states:

In view of *Fumihiro et al.*, which teach stable freeze dried preparations comprising vitamin B12 (and considering that methylcobalamin is the active form of vitamin B12) the skilled artisan would have reasonably predicted that a

freeze-dried preparation comprising methylcobalamin would possess enhanced stability and thus overcome the problems disclosed by *Hunik*.

As noted at specification page 3, lines 7-9, the inventors have discovered that methylcobalamin is more stable in a long term storage when in a preparation that contains at least one excipient that is in an amorphous freeze-dried solid form than in a crystalline freeze-dried solid. If desired, the methylcobalamin may also be in amorphous form.

The problem facing the inventors was not in stabilizing the preparation during the lyophilization, but rather, the long-term stability of preparations that contain methylcobalamin, especially preparations that contain only methylcobalamin, or a large amount of methylcobalamin. Much of the Examiner's analysis seems to focus on stabilization during the lyophilization process itself; however, that is not the problem facing the inventors.

The inventors have discovered that freeze-dried methylcobalamin, which is usually not stable when in long-term storage, can be stabilized when an amorphous excipient is also present in the preparation. The methylcobalamin itself does not need to be in an amorphous state (although it can be, if desired). It is sufficient if at least one or more of the species of the excipient are in an amorphous state (specification page 3, lines 10-13). Thus, the invention is achieved by an amorphous state of at least one component that is in combination with the methylcobalamin, and, optionally, by providing the methylcobalamin itself in an amorphous state.

*Banker*

Examiner cites Banker pages 394 and 399. Banker pages 394 and 399 are part of Chapter 12, "Parenteral Products." For the record, Chapter 12 in Banker is authored by James C. Boyland and Steven L. Nail. A complete copy of Chapter 12 is provided herewith in a supplemental Information Disclosure Statement.

Examiner's statement of reliance on Banker is simply a restatement of the problem that Applicants faced, that degradation is observed on storage. Examiner states "the skilled artisan would have reasonably predicted that a freeze-dried preparation comprising methylcobalamin would possess enhanced stability and thus overcome the problems disclosed by Hunik. However, the question is not whether the artisan would have been motivated to formulated methylcobalamin as a freeze-dried powder. Instead, the problem was that the long term stability of preparations of pure methylcobalamin was not good when the methylcobalamin was stored as a freeze-dried powder.

Banker page 399 teaches away from any suggestion that combining methylcobalamin with an amorphous substance would increase its stability in a freeze-dried preparation. Banker page 399 teaches away:

(1) by stating that there is a preference for crystallization over amorphous states;

(2) by explaining that some solutes may form a metastable amorphous phase initially on freezing and then crystallize when the material is heated. Mannitol is discussed as an example; and

(3) by discussing how to induce solutes that form metastable glassy systems upon freezing to crystallize (rather than stay in the metabstable glassy form). Banker discusses

the advantages of crystallization of the solute in terms of freeze-drying properties, as well as quality attributes of the final product.

Banker clearly places emphasis on providing freeze-dried preparations in which the components are in a crystalline state, not in an amorphous state.

Banker page 400, column 1, first paragraph, discusses amorphous excipients, however it is in the context of stabilization of protein drugs. Banker states:

> While crystallinity of a drug is generally desirable for freeze-drying, it is often important for excipients to remain amorphous. In particular, disaccharides (such as sucrose and trehalose) are important as formulation additives to stabilize proteins against damage caused by freezing, freeze-drying, or both. However, in order to be effective stabilizers, it is essential for these compounds to remain amorphous both during freeze-drying and during subsequent storage.

In addition, in the last full paragraph in column 1, Banker states:

> The use of maltose and lactose, also disaccharides, should be approached with caution, since they are both reducing sugars.

Banker is silent on stabilizing methylcobalamin. Banker does not specifically address methylcobalamin instability in freeze-dried preparations. Nor does Banker provide any chemical nexus between protein stabilization and stabilization of a methylcobalamin compound. Lastly, Banker leads away from use of a disaccharide such as maltose and lactose, by stating that they should be approached with caution.

*Fumihiro*

Fumihiro is silent as to how to solve the problem of the storage instability of methylcobalamin in a lyophylized preparation. Fuhimiro, uses a basic amino acid, such as histidine, arginine or lysine, in combination with 9 kinds of water-soluble essential vitamins.

Fumihiro states that mannitol or other sugar alcohol, lactose, maltose or other monosaccharide, oligosaccharide, can be used as a "diluting agent." However, it is not required that an excipient be present in amorphous form - and it is not suggested the excipient be in amorphous form. Fumihiro, by simply reciting the sugars, monosaccharides, and oligoccharides in a generic sense, does not recognize or suggest that the form of the diluting agent, even if it was an excipient, can be important. Fumihiro can only lead to the conclusion that the form of the sugar that is used as a diluting agent is not important, and to no conclusion as to the excipient.

Applicants discovered how to stabilize methylcobalamin even when it is in pure form, in a manner that does not require the addition of an amino acid or the addition of other vitamins. Thus, as to a freeze-dried preparation of methylcobalamin in combination with an excipient that is in amorphous form, Fumihiro, even in combination with the cited art, does not suggest the invention.

*Hunik*

Hunik is silent as to how to solve the problem of the storage instability of methylcobalamin in a lyophylized preparation.

Hunik discloses a fermentation process for the production of vitamin B12. At page 1, lines 23-26, Hunik acknowledges that methylcobalamin is known to be unstable in light in isolated form and is easily transformed to hydroxocobalamin in aqueous solution. Hunik notes that for that reason, almost all commercial vitamin B12 preparations consist of the "stable" cyanocobalamin form (page 1, lines 27-28). Hunik is silent on how to prepare a form of freeze-dried methylcobalamin that possess a long term storage stability.

Summary

As shown above, the combination of the cited art does not render obvious the invention in which freeze-dried methylcobalamin preparations are stabilized by the presence of an excipient in amorphous form.

***Makino, Craig***

In Office action paragraph 11, Examiner explained the Office's reliance on Makino and Craig:

> 4. Makino is relied on as disclosing that mannitol, lactose and the like are usable excipients in freeze-dried preparations comprising vitamins.
>
> 5. Craig is relied on as disclosing that sugars are well known excipients used as cyroprotectants during freeze-drying drug preparations.

*Makino*

Makino discloses a freeze-dried preparation comprising vitamin D3 that is unstable to light. Makino, column 2, lines 24-25 state that the excipients may include monosaccharides and disaccharides. However, Makino is silent as to use of an amorphous excipient to improve the long term storage of methylcobalamin preparations. In fact, by simply reciting monosaccharides, and disaccharides in a generic sense, Makino clearly does not recognize or suggest that the form of the excipient can be important. Makino can only lead to the conclusion that the form of the excipient is not important.

*Craig*

Craig is relied on as disclosing that sugars are well known excipients used as cyroprotectants **during** freeze-drying drug preparations [emphasis added]. As mentioned above, Applicants are concerned with the storage stability of methylcobalamin, not with the stability during freeze-drying.

Craig is silent as to use of the amorphous excipient, including sugar, for stabilization of the freeze-dried preparation comprising methylcobalamin, to protect methylcobalamin during storage as a freeze-dried product. In fact, Craig leads the artisan away from a reasonable expectation of success in reaching the invention. At page 193 (last lines) - page 194, Craig states:

> Given the potential advantages of preparing drugs in an amorphous form, the question arises as to why this approach is not used more often. The single most important reason is undoubtedly the problems associated with stability, both physical and chemical.

Thus Craig provides no motivation for an artisan faced with the problem of methylcobalamin instability in freeze-dried preparations to look to adding an excipient that is in amorphous form after the freeze-drying.

***Kim***

6. The sixth art document, Kim, is relied on as disclosing freeze-dried preparations comprising mannitol and a cosolute such as sucrose or lactose provide an amorphous excipient.

At Office action paragraph 12, Examiner states that in order to avoid vial breakage, the skilled artisan would have it *prima facie* obvious to include mannitol and a cosolute such as sucrose or lactose. However, vial breakage is not the problem that Applicants were attempting to solve, or the problem that Applicants solved. There is no nexus between storage instability of freeze-dried preparations of methylcobalamin and vial breakage. Kim is completely silent as to use of the amorphous excipient, including sugar, for stabilization of the freeze-dried preparation comprising methylcobalamin.

***The FDA Guide***

7. The seventh art document, the FDA Guide, is relied on as disclosing that one problem associated with lyophilized powders is poor solubility, increased time for reconstitution at the user stage may result in partial loss of potency if the drug is not completely dissolved, since it is common to use in-liner filters during administration to the patient.

The FDA Guide is silent on the use of an amorphous excipient, including sugar, for stabilization of the freeze-dried preparation comprising methylcobalamin. The FDA Guide is a review of the mechanics of lyophilization and sterilization. If anything, the FDA report would lead the artisan away from attempting to stabilize a substance that was unstable in long term storage after lyophilization by adding anything in amorphous form, or by lyophilizing in a manner that created an amorphous form. In the last paragraph before the glossary the Guide states:

> Manufacturers should be aware of the stability of lyophilized products which exhibit partial or complete meltback. Literature shows that for some products, such as the cephalosporins, that the crystalline form is more stable than the amorphous form of lyophilized product. The amorphous form may exist in the "meltback" portion of the cake where there is incomplete sublimation.

Nothing in the FDA Guide, even in combination with the other art, detracts from the patentability of the claimed invention.

***West***

> 8. The eighth art document, West, is relied on as disclosing amorphous vitamin B12 injections which comprise methylcobalmin thus allegedly indicating the feasibility of formulating amorphous methylcobalamin to one of ordinary skill in the art at the time the invention was made.

West is a 1948 paper. West is silent on stabilization of lyophilized preparations of methylcobalamin. West uses the word "amorphous" but it is not believed to be in the same context as Applicants' usage. West is attempting to characterize what is in the liver concentrates. West reports that four patients received single injections of "impure

amorphous" **liver** concentrates (see the header on West Table 1) that had 20,000 - 40,000 LLD units. An LLD unit was a measure of the presence of a factor that was required by *L. lactis* for growth, and that seem to correlate with the potency of a factor used to treat pernicious anemia. West does not disclose pure amorphous vitamin B12 injections which comprise methylcobalmin.

West compares the effect of injection of the impure amorphous liver concentrates with effect of injection of crystalline vitamin B12. Nothing in West, even in combination with the other art, detracts from the patentability of the claimed invention. The invention lies not in the preparation of an amorphous form of methylcobalamin. The invention is a way to increase the stability of methylcobalamin in freeze-dried preparations.

*Discussion*

Examiner's focus seems to be those aspects of the art that discuss maintaining the stability during the lyophilization process. However, the problem that Applicants were faced with was the long term storage instability of freeze-dried compositions that contained a high content of methylcobalamin, not the stability of methylcobalamin during the freeze-drying process.

As noted at specification page 15, last paragraph, the residual ratio of methylcobalamin as an active ingredient decreases due to degradation over time when stored under heated conditions; the appearance of the freeze-dried preparation markedly discolored. It is not desirable to use a preparation that exhibits discolor and that is

degraded. There is a high probability that such a preparation will exhibit cloudiness and precipitation during dissolution.

Applicants discovered that by providing the freeze-dried methylcobalamin in a preparation that contained an amorphous excipient, the long term storage of the freeze-dried methylcobalamin was greatly improved. Thus, for the first time, it was possible to provide a freeze-dried preparation of methylcobalamin that possess an enhanced long term storage stability, and was useful when high-concentrations of methylcobalamin therapy are needed.

The effect of the presence of an amorphous excipient is not predictable. As mentioned in the literature cited by the examiner, there are report that the presence of an amorphous form of a lyophilized product leads to instability of the product (See, for example, the discussion of the FDA report above).

All of the art is silent as to use of the amorphous excipient, including sugar, for stabilization of the storage of freeze-dried preparation comprising methylcobalamin. The deficiency in the cited art is not cured by the combination of the art. The combination of this art does not suggest to use of the amorphous excipient, including sugar, for stabilization of the freeze-dried preparation comprising methylcobalamin during storage after freeze-drying.

As demonstrated in the results shown in Figures 5 to 8, the presence of amorphous excipient in the freeze-dried preparation as claimed provides stable methylcobalamin. In addition, Figure 15 shows that, according to the invention,

methylcobalamin is more unstable in a crystalline environment than in an amorphous environment.

These advantageous results that can be obtained only with utilizing a preparation as claimed could not have been expected from the combination of the cited art. These unexpected results are respectfully believed to be sufficient to rebut the Examiner's art-based rejections. None of the above-mentioned advantages resulting from the combination of features recited in new claims 28 and 29 are disclosed, suggested or even hinted at in any of the cited documents.

The discussion above has demonstrated that the combination of the cited art do not establish *prima facie* obviousness. Accordingly, these rejections can be withdrawn.

***The Product by Process Claims***

In Office action paragraph 17, Examiner notes that certain claims are in product by process format. Applicants respectfully assert that the discussion above has shown that the product of the product by process claims is no obvious over the cited art. Accordingly, this rejection can be withdrawn.

## *Conclusion*

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the

Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn.

Applicants believe that a full and complete reply has been made to the outstanding Office action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.

Michele A. Cimbala
Attorney for Applicants
Registration No. 33,851

Date: May 19, 2009

1100 New York Avenue, N.W.
Washington, D.C. 20005-3934
(202) 371-2600

950027.1